

EXHIBIT 23



Filed on behalf of: Junior Party **UNIVERSITY
OF WESTERN AUSTRALIA**

Paper No. _____

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UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT TRIAL AND APPEAL BOARD

University of Western Australia,
Junior Party
(Patent 8,455,636,
Inventors: Stephen Donald Wilton, Sue Fletcher and Graham McClorey)

V.

Academisch Ziekenhuis Leiden,
Senior Party
(Application 11/233,495
Inventors: Garrit-Jan Boudewijn van Ommen, Judith Christina
Theodora van Deutekom, Johannes Theodorus den Dunnen and
Annemieke Aartsma-Rus).

Patent Interference No. 106,007 (RES)
(Technology Center 1600)

UNIVERSITY OF WESTERN AUSTRALIA MOTION 1
(For Judgment Under 35 U.S.C. § 112(a))

TABLE OF CONTENTS

I.	Precise Relief Requested.....	1
II.	Evidence in Support of the Motion.....	1
III.	Summary of the Argument.....	1
IV.	Factual Background	3
A.	Exon Skipping Therapies for DMD	3
B.	Exon Skipping Is Highly Unpredictable	4
C.	Disclosure of the AZL '495 Application	9
D.	Breadth of the AZL Claims.....	9
V.	Statement of Reasons for the Requested Relief.....	15
A.	Lack of Written Description Support for AZL's Claims	15
1.	The '495 Application Does Not Disclose Species that Are Representative of the Broad Genera Defined by the Independent Claims	17
2.	The '495 Application Does Not Disclose Structural Features Common to the Members of the Claimed Genera	19
3.	The Dependent Claims Do Not Narrow the Claims to Be Commensurate with the Scope of the Description.....	21
B.	The '495 Application Fails to Enable a Skilled Person to Make and Use the Invention Without Undue Experimentation.....	24
1.	Breadth of the Claims / Unpredictability of the Art	25
2.	Amount of Direction / Quantity of Experimentation.....	28
C.	The '495 Application Fails to Describe or Enable Therapeutic AONs	30
VI.	Conclusion	30

TABLE OF AUTHORITIES

	Page(s)
FEDERAL CASES	
<i>In re '318 Patent Infringement Litig.</i> , 583 F.3d 1317 (Fed. Cir. 2009).....	25
<i>AbbVie Deutschland GmbH & Co. v. Janssen Biotech, Inc.</i> , 759 F.3d 1285 (Fed. Cir. 2014).....	17, 18
<i>Ariad Pharm., Inc. v. Eli Lilly & Co.</i> , 598 F.3d 1336 (Fed. Cir. 2010) (<i>en banc</i>)	<i>passim</i>
<i>Brenner v. Manson</i> , 383 U.S. 519 (1966).....	30
<i>Centocor Ortho Biotech, Inc. v. Abbott Labs.</i> , 636 F.3d 1341 (Fed. Cir. 2011).....	30
<i>In re Curtis</i> , 354 F.3d 1347 (Fed. Cir. 2004).....	16, 17
<i>Enzo Biochem, Inc. v. Calgene, Inc.</i> , 188 F.3d 1362 (Fed. Cir. 1999).....	1, 26, 27
<i>Fiers v. Revel</i> , 984 F.2d 1164 (Fed. Cir. 1993).....	18, 21
<i>Genentech, Inc. v. Novo Nordisk A/S</i> , 108 F.3d 1361 (Fed. Cir. 1997).....	24
<i>Regents of the Univ. of California v. Eli Lilly & Co.</i> , 119 F.3d 1559 (Fed. Cir. 1997).....	15, 17, 21
<i>SuperGuide Corp. v. DirecTV Enterprises, Inc.</i> , 358 F.3d 870 (Fed. Cir. 2004).....	21
<i>In re Vaeck</i> , 947 F.2d 488 (Fed. Cir. 1991).....	26
<i>In re Wands</i> , 858 F.2d 731 (Fed. Cir. 1988).....	24
<i>Wyeth & Cordis Corp. v. Abbott Labs.</i> , 720 F.3d 1380 (Fed. Cir. 2013).....	29

FEDERAL STATUTES

35 U.S.C. § 112(a)1, 15, 24

REGULATIONS

37 C.F.R. § 41.121(a)(1)(iii).....1

1 **I. Precise Relief Requested**

2 Pursuant to 37 C.F.R. § 41.121(a)(1)(iii), the University of Western Australia (“UWA”)
3 requests entry of judgment that Academisch Ziekenhuis Leiden’s (“AZL”) Application No.
4 11/233,495 (“the ’495 application”) fails to provide adequate written description support for,
5 and/or fails to enable, AZL’s involved claims as required by 35 U.S.C. § 112(a).

6 **II. Evidence in Support of the Motion**

7 Appendix 1 is a list of exhibits cited in support of this motion. The requirement for a
8 statement of material facts has been waived. (*See* Paper 19 at 5.)

9 **III. Summary of the Argument**

10 When the competing applications in this interference were filed, a handful of specific
11 operative exon skipping antisense oligonucleotides (“AONs”) targeting exon 53 had been
12 discovered, and the path to identifying others was largely unknown. Both parties submitted
13 broad generic claims in the hope that identification of broader families of operative AONs would
14 follow predictably from those narrower discoveries. Subsequent experience has revealed that
15 operative sequences are actually highly unpredictable, varying with parameters such as
16 nucleobase sequence, length, backbone chemistry, and internucleotide linkages. Experience with
17 exon skipping is consistent with the now familiar challenges with antisense technology
18 generally. *See, e.g., Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1372 (Fed. Cir. 1999)
19 (“[A]ntisense strategies have not been as universally straightforward or as easy to apply as was
20 initially hoped”) Accordingly, UWA brings this motion challenging the patentability for
21 the full breadth of AZL’s claims under the written description and enablement requirements.

22 The involved claims of AZL’s ’495 application are directed to AONs capable of inducing
23 the cellular splicing machinery to “skip” exon 53 of the dystrophin gene during processing of the
24 dystrophin pre-mRNA. At the filing date of the ’495 application, exon skipping was very much

1 a developing technology, with small changes to the chemical structure of an AON resulting in
2 significant and unpredictable effects. Despite this, each of the involved claims of the '495
3 application potentially encompasses hundreds of billions, trillions, or incalculable numbers of
4 chemically distinct AONs (depending on the claim and how it is interpreted). Yet the '495
5 application discloses only a single AON allegedly capable of inducing exon 53 skipping, and
6 fails to disclose any common structure correlating with that function. AZL's claims are therefore
7 unpatentable because they lack written description support.

8 AZL's claims are also invalid because the '495 application does not enable a person of
9 skill in the art to make and use the full scope of the claimed invention without undue
10 experimentation. The involved claims encompass variations to AON length; a tremendous
11 number of possible nucleobase sequences; extensive variation to the chemical backbone and
12 internucleotide linkages; "mismatches" with the target sequence; and the use of non-natural
13 bases. In this unpredictable field, where each AON needs to be empirically tested, the quantity
14 of experimentation needed to make and use the claimed invention is undue. AZL's involved
15 claims are therefore also unpatentable for lack of enablement.

16 Notably, the sole disclosed utility for the claimed AONs is the treatment of patients with
17 Duchenne Muscular Dystrophy ("DMD"), and AZL's claims cover therapeutic AONs. But no
18 exon skipping therapy has ever been approved. And the '495 application does not provide, either
19 in its specification or by way of an accompanying declaration, any clinical data or other proof of
20 therapeutic *in vivo* activity. Development of a therapeutic exon skipping AON has and will
21 require an immense investment of time, energy, money, and experimentation—and overcoming
22 challenging drug delivery issues that have plagued antisense technologies since their inception.

1 **IV. Factual Background**

2 **A. Exon Skipping Therapies for DMD**

3 DMD is a neuromuscular genetic disease that occurs in one in every 3,500 boys born
4 worldwide. Patients with DMD produce little or no dystrophin in their muscle. (Exh. 2081 at ¶
5 13.) Without dystrophin, normal activity causes excessive damage to muscle cells. DMD is
6 invariably fatal. (Exh. 2081 at ¶ 15.)

7 DMD is caused by mutations in the dystrophin gene that prevent synthesis of fully
8 functional dystrophin protein. (Exh. 2081 at ¶¶ 16-18.) Another disease, called Becker
9 Muscular Dystrophy (“BMD”), also results from mutations in the dystrophin gene, but patients
10 display a later, and much slower, rate of disease progression. While many BMD patients carry
11 mutations that result in loss of a substantial portion of the dystrophin protein, they nevertheless
12 produce dystrophin that functions sufficiently to provide a milder form of the disease. (Exh.
13 2081 at ¶¶ 20-22.)

14 To treat DMD, scientists have investigated “exon skipping” as a means to generate a
15 functional, though shorter, form of the dystrophin protein, similar to dystrophin protein found in
16 BMD patients. (Exh. 2081 at ¶ 23.) These treatments seek to use AONs to interfere with the
17 splicing of the dystrophin pre-mRNA. By skipping targeted exons, the cellular machinery is able
18 to translate the RNA into a functional form of dystrophin. (Exh. 2081 at ¶¶ 42-48.)

19 Different types of AON have been studied as tools for exon skipping. These include
20 AONs of varying lengths with chemically modified nucleobases, backbones (corresponding to
21 the ribose portion of RNA), and internucleotide linkages. (Exh. 2081 at ¶¶ 51-63.) Prominent
22 among these are phosphorothioates (“PS”), often in combination with the substitution of a
23 methyl group for a hydrogen atom attached to the oxygen atom at the 2’ position of the ribose
24 ring (“2’-O-Me-PS”); morpholinos (“PMOs”), peptide nucleic acids (“PNAs”), and linked

1 nucleic acids (“LNAs”). Researchers have also experimented with “chimeric” or “hybrid”
2 AONs containing multiple different types of chemical modifications, such as “gapmers”
3 containing a central region of 2’-O-Me-PS nucleotides flanked by LNAs. (Exh. 2081 at ¶ 64.)

4 The Food and Drug Administration (“FDA”) has yet to approve an exon skipping
5 therapy. (Exh. 2081 at ¶ 87.) Despite more than 30 years of research, only one antisense
6 treatment is currently FDA approved for marketing in the U.S. (Exh. 2081 at ¶ 88.)

7 **B. Exon Skipping Is Highly Unpredictable**

8 It is now known that many factors influence the binding of an AON to its target,
9 including AON length, target accessibility, nucleobase sequence, modifications to the chemical
10 backbone, Watson-Crick “mismatches,” and modifications to the internucleotide linkages.
11 Consequently, there is tremendous variability and unpredictability in the efficacy of different
12 AONs targeted to different regions of the dystrophin pre-mRNA, and each different AON needs
13 to be empirically tested.

14 In 2001, the AZL co-inventors reported that “[t]he efficacy of AONs is largely
15 determined by their binding affinity for the target sequence . . . *it is difficult to predict which*
16 *AONs are capable of binding the target sequence.*” (Exh. 2012 at 1548; Exh. 2081 at ¶ 69.¹) In
17 2002, the AZL group concluded that they “*have no insight* into the actual position of the
18 targeted sequence within the completely folded RNA structure. Its accessibility, and thus *the*
19 *effectivity of any designed AON, will therefore still have to be tested empirically in the cells*, as
20 was done in this study.” (Exh. 2010 at S76; Exh. 2081 at ¶ 70.)

21 And this did not change after AZL’s PCT/NL03/00214 application was filed in 2003, or
22 the ’495 application involved in the current interference was filed in 2005. A 2007 publication

¹ Unless otherwise indicated, all emphases are added.

co-authored by members of the AZL and UWA groups explained that “several years after the first attempts at dystrophin exon skipping with AOs [AONs], *there are still no clear rules to guide investigators in their design*, and in mouse and human muscle cells *in vitro there is great variability for different targets and exons.*” (Exh. 2013 at 807; Exh. 2081 at ¶ 71.) Even as late as 2009, the AZL group wrote that “*a trial and error procedure* is still involved to identify potent AONs.” (Exh. 2014 at 548; Exh. 2081 at ¶ 72.)

A 2011 article by Wu and co-workers highlights this unpredictability. These researchers screened a series of AONs covering more than two-thirds of human dystrophin exon 50 and two flanking intron sequences. A subset of the tested AONs having overlapping nucleobase sequences, all made with 2’-O-Me-PS chemistry, is shown in the table below:

Name	Target ²	2’-O-Me-PS AON Sequence	Length	Effect
AO3PS	-19+1	UCUUUAAACAGAAAAGCAUAC	20	-
AO4PS	-19+3	CCUCUUUAAACAGAAAAGCAUAC	22	4%
AO5PS	-19+8	AACUUCUCUCUUUAAACAGAAAAGCAUAC	27	21%
AO6PS	-19+13	CUUCUAAACUUCUCUCUUUAAACAGAAAAGCAUAC	32	3%

(Exh. 2015 at 4; Exh. 2081 at ¶ 74.) The 20-mer AO3PS induced no detectable exon skipping. The 22-mer AO4PS, differing only in having two additional nucleotides complementary to the *DMD* gene, induced detectable exon skipping, but only in 4% of cells. Adding an additional five nucleotides increased exon skipping to 21%. However, adding five more nucleotides largely abrogated this effect. (Exh. 2081 at ¶ 74.)

A 2009 article from Heemskerk and co-workers, published years after the AZL ’495 application was filed in 2005 or the PCT application was filed in 2003, also highlights this

² The Target column shows the coordinates of the target site relative to the pre-mRNA sequence. “+” represents an exonic position and “-” represents an intronic position, with the numbers representing the first and last nucleotides of the AON target sequence. (Exh. 2015 at 4.)

unpredictability. (Exh. 2020 at 259-60; Exh. 2081 at ¶ 75.) Heemskerk analyzed exon skipping by RT-PCR of mouse exon 23 with a “short” 2’-O-Me-PS AON that was 20 nucleotides in length, a “long” 2’-O-Me-PS AON that was 25 nucleotides in length, and a “long” AON made with a morpholino (PMO) backbone. The sequences of these AONs are shown below.

Name	AON Sequence (3’ to 5’)	Length
m23AON5’s	UCCAUUCGGCUCCAAACCGG	20
m23AON5’slong	UAAAGUCCAUUCGGCUCCAAACCGG	25
m23PMO5’s	TAAAGTCCATTTCGGCTCCAAACCGG	25

According to the authors, “[t]he PMO induces significantly higher levels of exon skipping than both [2’-O-Me-PS] AONs.” (Ex. 2020 at 259; Exh. 2081 at ¶ 75.) But “[t]he long [2’-O-Me-PS] is significantly less efficient than the short version.” (Ex. 2020 at 259; Exh. 2081 at ¶ 75.) These data show the complex interactions between nucleotide length, nucleotide sequence, internucleotide linkages, and chemical backbone, and reinforces the need for empirically testing each chemically distinct AON. (Exh. 2081 at ¶ 75.)

Arechavala-Gomez and colleagues investigated eight specific AON sequences targeting human DMD exon 51 in two different chemical forms (2’-O-Me-PS and morpholino) in human muscle cells, human muscle explants, and human muscle explants from patients with DMD. (Exh. 2013 at 798.) Five AONs targeting the 5’ splice site were “surprisingly” determined to be largely ineffective at inducing skipping of exon 51. (Exh. 2013 at 803; Exh. 2081 at ¶ 77.) Three other overlapping sequences complementary to portions of exon 51 were each capable of inducing exon 51 skipping in cells from healthy patients, including sequence B30 (targeting +66+95) and A20 (targeting +68+87). (Exh. 2013 at 803; Exh. 2081 at ¶ 77.) But B30 induced significantly better exon skipping than A20 in cells derived from a DMD patient with a deletion in exons 48 to 50. (Exh. 2013 at 805 (“the skip achieved with AO A20 was less efficient”); Exh. 2081 at ¶ 77.) Similarly, B30 induced significantly better skipping than A20 in cells derived

1 from a DMD patient with a deletion in exon 50. (Exh. 2013 at 805 (“the percentage of the skip
2 was 13% for AO[N] A20 and 73% for AO[N] B30”); Exh. 2081 at ¶ 77) This shows that both
3 target cell type and nucleobase sequence influence exon skipping. (Exh. 2081 at ¶ 77.)

4 The unpredictability of exon skipping occurs in part because of a “Goldilocks” dilemma.
5 If the AON does not bind tightly enough, exon skipping will not occur. But exon skipping also
6 will not occur if the AON binds too tightly, because AON turnover from transcript to transcript
7 is essential. (Exh. 2081 at ¶¶ 50, 74-75; Exh. 2014 at 552; Exh. 2020 at 259.) Moreover,
8 because the AON needs to access conformationally complex “target” sequences, changes in
9 length have unpredictable effects. (Exh. 2081 at ¶¶ 69-70.) As AZL explained to the European
10 Patent Office in June 2014, “a longer [AON] is not per definition more efficient than a shorter
11 counterpart [AON]. Other parameters, such as the content and/or context of the additional target
12 sequence, may play a role.” (Exh. 2085 at 1.)

13 While *in vitro* exon skipping is unpredictable, there are significant additional challenges
14 with the use of AONs in treating patients, including confirmation of drug delivery. (Exh. 2081 at
15 ¶¶ 87-108.) For DMD, the design of the AON must allow effective systemic delivery to the
16 nuclei of cells in at least skeletal muscle and cardiac muscle, but this remains a significant
17 hurdle. (Exh. 2081 at ¶ 90.) In 2002, the AZL group explained that “*theoretically*” targeted
18 exon skipping “*may be* therapeutically applicable.” (Ex. 2010 at S71; Exh. 2081 at ¶ 92.) In a
19 2003 publication presenting much of the same information disclosed in the AZL applications, the
20 AZL group explained that their results had therapeutic potential “*provided that a suitable means*
21 *of administration for the AONs is developed. . . .*” (Exh. 2018 at 911; Exh. 2081 at ¶ 92.) A
22 2013 review article characterized AON drug delivery as a “significant and ever present
23 challenge.” (Exh. 2005 at 179; Exh. 2081 at ¶ 96.) And a review published in April of this year

1 states that “an improved understanding of the *in vivo* barriers to oligo delivery” is needed before
2 large-scale clinical successes can be obtained. (Exh. 2022 at 7; Exh. 2081 at ¶ 97.)

3 Actual clinical experience with exon skipping in DMD highlights the unpredictability of
4 therapeutic efficacy. (Exh. 2081 at ¶¶ 109-19.) Two companies have initiated human clinical
5 trials to treat DMD using exon skipping. The first, Sarepta, is investigating an exon 51 targeted
6 morpholino AON, described by the UWA inventors, having the following nucleobase sequence:
7 CTCCAACATCAAGGAAGATGGCATTCTAG. (Exh. 2032; Exh. 2033 at 3; Exh. 2081 at
8 ¶¶ 110.) This drug candidate, called eteplirsen or AVI-4658, produced a statistically significant
9 increase in novel dystrophin-positive fibers after 24 weeks of treatment, as well as a statistically
10 significant clinical benefit of 69 meters. (Exh. 2032.) More recent data show a statistically
11 significant, clinically meaningful treatment benefit of 75.1 meters ($p \leq 0.004$) for the eteplirsen
12 group over a control group at week 144. (Exh. 2081 at ¶ 113; Exh. 2059 at slide 9.) Eteplirsen is
13 **not** disclosed in the AZL applications.

14 The second, Prosensa, is investigating a 2'-O-Me-PS AON called drisapersen and
15 disclosed as h51AON1 in the AZL applications. (Exh. 2036 at 1513; Exh. 2037 at 987.) The
16 nucleobase sequence of the Prosensa sequence targets a region of exon 51 similar to that targeted
17 by eteplirsen, but the Prosensa drug candidate is shorter (20 nucleotides in length versus 30), has
18 a different chemical backbone and internucleotide linkages, and contains “U” nucleobases in
19 place of “T” nucleobases. (Exh. 2081 at ¶ 115.) Despite some sequence similarities to
20 eteplirsen, Prosensa’s phase III study **failed** to meet the primary endpoint of a statistically
21 significant improvement in the 6MWT compared to placebo. (Exh. 2039; Exh. 2081 at ¶¶ 117-
22 18.) There was also no treatment difference in key secondary assessments of motor function,

1 including the 10-meter walk/run test, 4-stair climb, and North Star Ambulatory Assessment.
2 (Exh. 2039; Exh. 2081 at ¶¶ 117, 431.)

3 **C. Disclosure of the AZL '495 Application**

4 The '495 application is directed to the targeted skipping of exons to convert a DMD
5 phenotype into a milder BMD phenotype. (Exh. 2041 at [0015]; Exh. 2081 at ¶ 143.) However,
6 only a single AON, h53AON1, is purported to induce skipping of exon 53 *in vitro* (another AON
7 was targeted against exon 53 but failed). (Exh. 2041 at 15, Table 2; Exh. 2081 at ¶ 158.)

8 h53AON1, like all of the other AONs disclosed in the '495 application, is a 2'-O-Me-PS
9 that contains exclusively the natural nucleobases A, C, G, and U. (Exh. 2081 at ¶ 155; Exh.
10 2041 at [0047].) h53AON1 is only 18 nucleotides in length; the longest AON tested against any
11 exon was only 24 nucleotides. (Exh. 2041 at 15, Table 2; Exh. 2081 at ¶¶ 156-57.) Although all
12 are claimed, no morpholino, LNA, PNA, or hybrid AONs are disclosed. (Exh. 2081 at ¶ 417.)
13 Similarly, no AONs (not even a 2'-O-Me-PS) containing a "mismatch" versus the target
14 pre-mRNA sequence is disclosed. (Exh. 2081 at ¶ 137.)

15 While the AZL applications purport to be directed to therapies for DMD, no clinical data
16 is provided in the specification, or by declaration in the file history, demonstrating therapeutic
17 efficacy. (Exh. 2081 at ¶ 420.)

18 **D. Breadth of the AZL Claims**

19 In contrast to the single disclosed AON purportedly capable of inducing *in vitro* skipping
20 of exon 53, the AZL claims at issue potentially encompass tremendous numbers of compounds.
21 (Exh. 2081 at ¶¶ 189-226.) The claims generally come in two flavors: the "comprising" claims
22 that claim broadly based upon a kernel of common structure; and the "capable of binding" claims
23 that are in essence purely functional claims. (Exh. 2081 at ¶ 188.)

Independent claims 15 and 76 are both “comprising” claims. For convenience, underlining is used to show the terms that differ between these claims:

15. An isolated antisense oligonucleotide of 15 to 80 nucleotides comprising at least 15 bases of the sequence cuguugccuccgguucug (SEQ ID NO: 29), wherein said oligonucleotide induces exon 53 skipping in the human dystrophin pre-mRNA, said oligonucleotide comprising a modification selected from the group consisting of: 2'-O-methyl, 2'-O-methyl-phosphorothioate, a morpholine ring, a phosphorodiamidate linkage, a peptide nucleic acid and a locked nucleic acid.

76. An isolated antisense oligonucleotide of 18 to 80 nucleotides comprising at least the base sequence of the sequence cuguugccuccgguucug (SEQ ID NO: 29), wherein said oligonucleotide induces exon 53 skipping in the human dystrophin pre-mRNA, said oligonucleotide comprising a modification selected from the group consisting of: 2'-O-methyl, 2'-O-methyl-phosphorothioate, a morpholine ring, a phosphorodiamidate linkage, a peptide nucleic acid and a locked nucleic acid.

(Exh. 2045 at 1.)

A tremendous number of compounds are included within the scope of the claims. (Exh. 2081 at ¶¶ 191-99.) Claim 15 encompasses AONs that vary in length from 15 to 80 nucleotides, while claim 76 encompasses AONs that vary in length from 18 to 80 nucleotides. Claim 15 requires that the claimed AON include 15 of the 18 nucleobases of SEQ ID NO: 29, while claim 76 requires that the claimed AON include all 18 of those nucleobases. The nucleobase sequence of the remaining nucleotides is undefined. (Exh. 2081 at ¶ 191.)

If one limits the nucleobases to those found in RNA as shown in SEQ ID NO: 29 (A, C, G, and U), adding a single nucleobase to a 15-mer yields 8 possible sequence combinations. (Exh. 2081 at ¶ 192.) Adding two nucleobases yields 64 possible combinations. Adding 35 nucleobases to obtain a 50-mer yields 42,501,298,345,826,806,923,264 possible combinations. Adding 55 nucleobases to obtain an 80-mer yields

72,692,156,019,487,586,799,426,948,609,081,344 possible combinations.³ (Exh. 2081 at ¶ 192.)

Of course, this significantly *underestimates* the number of possible nucleobase combinations within the scope of these claims, because claims 15 and 76 are not limited to the “natural” bases A, C, G, and U found in RNA, but also include thymine (T) (a nucleobase found in DNA) and other naturally occurring and non-naturally occurring nucleobases such as 5-methyl-cytosine, inosine, hypoxanthine, xanthine, and many others. (Exh. 2081 at ¶ 193.)

Claims 15 and 76 *also* allow tremendous variation in the chemical backbone and internucleotide linkages, as they require only “a modification selected from the group consisting of: 2’-O –methyl, 2’-O-methyl-phosphorothioate, a morpholine ring, a phosphorodiamidate linkage, a peptide nucleic acid and a locked nucleic acid.” There is no requirement in these claims that the AON include a single “modification” to the exclusion of the others. Nor is there any requirement in the claim that all of the nucleotides in the AON contain a modification or the same modification if different types of modifications are present. (Exh. 2081 at ¶¶ 194-99.)

This again leads to tremendous breadth. If one conservatively assumes that a single position in the AON is fixed (with, for example, a morpholine ring) and the remaining positions in the AON contain any of a 2’-O-Me, a 2’-O-Me-PS, a morpholine ring, a LNA, or a PNA, then the number of possible modifications to the chemical backbone is immense. For example, an 18-mer would contain 5^{17} possible chemical modifications, and a 50-mer would contain 5^{49} possible chemical modifications. (Exh. 2081 at ¶ 196.) Again, however, this underestimates the possible

³ Assuming only the four RNA nucleobases, the number of nucleobase combinations for a particular length AON can be calculated by the following formula, where “n” equals the number of bases being added to the chain: $(4^n) \times (n+1)$. This is because each additional nucleotide can be added to either end of the SEQ ID NO: 29 sequence. (Exh. 2081 at 60 n. 4.)

1 number of combinations, because the claim is open to *any* possible chemical modification to the
2 chemical backbone and to the internucleotide linkages, provided that the AON contains a single
3 modification from the recited list. (Exh. 2081 at ¶ 196.) Thus, the immense breadth of these
4 claims is derived from (1) the varying ranges of possible AON length; (2) the immense number
5 of possible nucleobase sequence combinations; (3) the potential for an unspecified number of
6 “mismatches” with the target sequence; (4) the immense number of possible chemical backbone
7 and internucleotide linkage combinations; (5) the possibility of non-natural bases; and (6) the
8 potential for other chemical modifications.

9 Independent claims 78 and 100 are “capable of binding” claims, and if anything are even
10 broader. They state as follows:

11 78. An isolated antisense oligonucleotide of 18 to 50 nucleotides in length,
12 wherein said oligonucleotide is capable of binding to an exon-internal sequence of
13 exon 53 of the human dystrophin pre-mRNA and inducing skipping of exon 53,
14 and wherein h53AON1 (cuguugccuccgguucug) (SEQ ID NO: 29) is capable of
15 binding to said exon-internal sequence of exon 53 pre-mRNA, said
16 oligonucleotide comprising a modification selected from the group consisting of:
17 2’-O-methyl, 2’-O-methyl-phosphorothioate, a morpholine ring, a
18 phosphorodiamidate linkage, a modification to increase resistance to RNaseH, a
19 peptide nucleic acid and a locked nucleic acid.

20 100. An isolated antisense oligonucleotide of 18 to 50 nucleotides in length,
21 wherein said oligonucleotide is complementary to a consecutive part of between
22 16 and 50 nucleotides of an exon-internal sequence of exon 53 of the human
23 dystrophin pre-mRNA and is capable of inducing skipping of exon 53, and
24 wherein h53AON1 (cuguugccuccgguucug) (SEQ ID NO: 29) is capable of
25 binding to said exon-internal sequence of exon 53 pre-mRNA, said
26 oligonucleotide comprising a modification selected from the group consisting of:
27 2’-O-methyl, 2’-O-methyl-phosphorothioate, a morpholine ring, a
28 phosphorodiamidate linkage, a modification to increase resistance to RNaseH, a
29 peptide nucleic acid and a locked nucleic acid.

30 (Exh. 2045 at 1-3.)

31 Neither of these claims recites *any* particular nucleobase sequence that must be included
32 within the claimed AON. (Exh. 2081 at ¶ 208.) Instead, claim 78 requires that the claimed AON

1 be “capable of binding” to an undefined “exon-internal sequence” to which h53AON1 is also
2 “capable of binding.” Claim 100 requires that the claimed AON be “complementary to a
3 consecutive part of between 16 and 50 nucleotides” of an undefined “exon-internal sequence”
4 that is “capable of binding” h53AON1. (Exh. 2081 at ¶¶ 208, 216.)

5 Because “exon-internal sequence” is undefined, it is unclear whether the claimed AON
6 needs to bind to (1) the entire portion of exon 53 bound by h53AON1; (2) an overlapping portion
7 of exon 53 bound by h53AON1 (i.e., some but not all of the nucleotides bound by h53AON1); or
8 (3) any portion of exon 53 that is not a splice site for the exon. (Exh. 2081 at ¶¶ 210-12, 216.) It
9 is also unclear how one assesses the conditions under which binding is to occur. This is a serious
10 deficiency, as AON binding is affected by temperature, ion concentration, and cell type, among
11 other things. (Exh. 2081 at ¶¶ 213, 216.) For claim 78, this is exponentially complicated by the
12 nesting of two separate “capable of binding” limitations (one for the claimed AON and one for
13 h53AON1). (Exh. 2081 at ¶ 211.)

14 But even if one conservatively assumes that the AON needs to bind to the entire portion
15 of exon 53 bound by h53AON1 (or 16 nucleotides of it for claim 100), there are still a
16 tremendous number of compounds within the scope of the claim for the reasons explained above
17 for the “comprising” claims. In particular, there are a tremendous number of possible nucleobase
18 combinations, chemical backbones, and internucleotide linkages, the potential for mismatches,
19 and the possibility of non-natural bases. (Exh. 2081 at ¶¶ 214, 216-17.)

20 The dependent claims do not meaningfully limit the scope of the independent claims.
21 (Exh. 2081 at ¶¶ 218-26.) Claims 77 (18 nucleotides), 101 (less than 50 nucleotides), and 102
22 (less than 80 nucleotides) limit the length of the claimed AON. (Exh. 2045 at 1, 3.) As an initial
23 matter, the length limitations of claims 101 and 102 still allow for tremendous numbers of

1 possible nucleobase combinations, as they shorten the possible AONs by only a single
2 nucleotide. And each of claims 77, 101, and 102 fails to limit in any way the possible
3 “modifications” to the chemical backbone and internucleotide linkages, and therefore still
4 encompass hundreds of billions or trillions of possible compounds. (Exh. 2081 at ¶¶ 200, 225,
5 299, 309.)

6 Claim 88 defines certain parameters for assaying skipping, and claims 89 (RT-PCR
7 and/or sequence analysis) and 90 (immunohistochemical and/or Western blot analysis) recite
8 certain tests for detecting skipping. (Exh. 2045 at 2.) But none of claims 88-90 provide any
9 structural limitations in terms of length, nucleobase sequence, mismatches, chemical backbone,
10 or internucleotide linkages, such that these claims similarly encompass tremendous numbers of
11 possible compounds. (Exh. 2081 at ¶¶ 222, 307.)

12 Claims 82 (2'-O-methyl, 2'-O-methyl phosphorothioate), 84 (morpholine ring and
13 phosphorodiamidate linkage), and 86 (morpholine phosphorodiamidate) limit the modifications
14 to the chemical backbone (Exh. 2045 at 2), but do not provide any additional limitations in terms
15 of length, nucleobase sequence, or mismatches (Exh. 2081 at ¶ 221). Claims 82 and 84 also
16 only require a single modification to the chemical backbone. (Exh. 2081 at ¶¶ 219-20.)

17 Claim 97 (DNA bases or RNA bases) limits the AON to the natural bases A, C, G, T, and
18 U, but does not provide any additional limitation in terms of length, nucleobase sequence,
19 mismatches, chemical backbone, or internucleotide linkages. (Exh. 2045 at 3; Exh. 2081 at
20 ¶¶ 223-24.) Claim 98 depends from claims 15, 76, 77, 78, or 100, and limits the AON to
21 “RNA.” (Exh. 2045 at 3.) As an initial matter, this is inconsistent with the requirement in these
22 claims that the AON contain “a modification” not found in RNA. In any case, claim 98 does not

1 provide any additional limitation for length, mismatches, or nucleobase sequence. (Exh. 2081 at
2 ¶¶ 223-24.)

3 Claims 79, 80, and 103 all address the complementarity of the AON nucleobase sequence
4 with exon 53. (Exh. 2045 at 2-3.) Claim 79 depends from claim 78, and requires that the “exon-
5 internal sequence” contain a “consecutive part of between 16 and 50 nucleotides” of exon 53,
6 and that the AON is complementary to that part. (Exh. 2045 at 2.) Claim 80 depends from claim
7 15, and requires that the AON be complementary to exon 53. (Exh. 2045 at 2.) Claim 103
8 depends from claims 78 or 100, and provides that the AON is capable of binding without
9 mismatches to the exon-internal sequence. (Exh. 2045 at 3.) None of these claims place any
10 additional limitations on AON length, chemical backbone, internucleotide linkages, or the use of
11 non-natural bases. Nor do these claims provide further guidance concerning the binding of
12 h53AON1 relative to the claimed AONs. (Exh. 2081 at ¶¶ 201-05, 218, 226, 319-20, 322.)

13 In sum, none of the dependent claims place meaningful limits on length, nucleobase
14 sequence, *and* the chemistry of the backbone and internucleotide linkages, and consequently all
15 of the claims encompass tremendous numbers of possible chemical compounds.

16 **V. Statement of Reasons for the Requested Relief**

17 **A. Lack of Written Description Support for AZL’s Claims**

18 The test for compliance with the written description requirement of 35 U.S.C. § 112(a)
19 “is whether the disclosure of the application relied upon reasonably conveys to those skilled in
20 the art that the inventor had possession of the claimed subject matter as of the filing date.” *Ariad*
21 *Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). When claims
22 are directed to a genus, “a sufficient description . . . requires the disclosure of either [1] a
23 representative number of species falling within the scope of the genus or [2] structural features
24 common to the members of the genus so that one of skill in the art can “visualize or recognize”

1 the members of the genus.” *Id.* at 1350 (citing *Regents of the Univ. of California v. Eli Lilly &*
2 *Co.*, 119 F.3d 1559, 1568-69 (Fed. Cir. 1997)). While functional language can meet the written
3 description requirement when there is an established correlation between structure and claimed
4 function, “merely drawing a fence around the outer limits of a purported genus is not an adequate
5 substitute for describing a variety of materials constituting the genus and showing that one has
6 invented a genus and not just a species.” *Id.* at 1350. When evaluating written description
7 support for generic claims, factors to be considered include the existing knowledge in the
8 particular field, the extent and content of the prior art, the maturity of the science or technology,
9 and the predictability of the technology at issue. *Id.* at 1351.

10 AZL’s claims are directed to the nascent and highly unpredictable technology of exon
11 skipping AONs intended for therapeutic use. (*See* § IV.D, above; Exh. 2081 at § IV.F-H.)
12 These claims are exceedingly broad, encompassing tremendous numbers of potential
13 compounds, and rely on functional language to define the claimed genera. Despite this breadth
14 and the unpredictability of exon skipping, the ’495 application (and the earlier-filed AZL PCT
15 application) discloses just a single species of AON allegedly capable of inducing *in vitro*
16 skipping of exon 53, and identifies no structural features common to the members of the genus.
17 (Exh. 2081 at ¶¶ 121, 278, 294-326.) “[A] patentee will not be deemed to have invented species
18 sufficient to constitute the genus by virtue of having disclosed a single species when ... the
19 evidence indicates ordinary artisans could not predict the operability in the invention of any
20 species other than the one disclosed.” *In re Curtis*, 354 F.3d 1347, 1358 (Fed. Cir. 2004).
21 Accordingly, as explained below, the Board should grant this motion and hold AZL’s claims
22 unpatentable.

1 **1. The '495 Application Does Not Disclose Species that Are**
2 **Representative of the Broad Genera Defined by the Independent**
3 **Claims**

4 The '495 application discloses only a single AON purportedly capable of inducing *in*
5 *vitro* skipping of exon 53. (Exh. 2041 at 15, Table 2; Exh. 2081 at ¶ 278.) That single species
6 fails to adequately support AZL's broad genus claims.

7 Exon skipping of dystrophin pre-mRNA was a nascent and highly unpredictable
8 technology as of the time of the invention (and remains so today), as demonstrated by
9 publications from investigators in the field (Exh. 2015 at 8; Exh. 2017 at 644), publications by
10 the AZL applicants (Exh. 2012 at 1548; Exh. 2013 at 807; Exh. 2014 at 548; Exh. 2018 at 911;
11 Exh. 2020 at 259-60; Exh. 2024 at 238; Exh. 2025 at 450), AZL's submissions to other patent
12 offices (Exh. 2042 at 29, 49; Exh. 2085 at 1; Exh. 2084 at 3), and the disclosure of the '495
13 application itself (Exh. 2041 at [0051], Table 2). Given this unpredictability, a skilled person
14 would need to empirically determine whether any given AON encompassed by claims 15, 76, 78,
15 or 100 would be capable of inducing skipping of exon 53. (Exh. 2081 at ¶¶ 280-326.)

16 Disclosure of h53AON1 is insufficient to provide a description of the full scope of AZL's
17 independent claims. *E.g. In re Curtis*, 354 F.3d at 1358 (disclosure of a single species within a
18 claimed genus will not convey possession of the genus when evidence indicates that ordinary
19 artisans could not predict the operability in the invention of any species other than the one
20 disclosed); *Eli Lilly*, 119 F.3d at 1568 ("A description of rat insulin cDNA is not a description of
21 the broad classes of vertebrate or mammalian insulin cDNA."); *AbbVie Deutschland GmbH &*
22 *Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1301 (Fed. Cir. 2014) ("Functionally defined genus
23 claims can be inherently vulnerable to invalidity challenge for lack of written description
24 support, especially in technology fields that are highly unpredictable, where it is difficult to
25 establish a correlation between structure and function for the whole genus or to predict what

1 would be covered by the functionally claimed genus.”). Claiming all AONs “that achieve a
2 result without defining what means will do so is not in compliance with the description
3 requirement; it is an attempt to preempt the future before it has arrived.” *Fiers v. Revel*, 984 F.2d
4 1164, 1171 (Fed. Cir. 1993).

5 Even if the Board were to conclude that the design of exon skipping AONs would have
6 been a predictable undertaking for persons of ordinary skill as of March 2003 or September
7 2005, disclosure of h53AON1 would still be insufficient to provide description supporting the
8 full scope of the claims. The independent claims in the ’495 application potentially encompass a
9 tremendous number of different chemical compounds. While AZL has attempted to stake out the
10 boundaries of its claimed genera, only a single species is described, and the task of identifying
11 additional species falling within the claims is left entirely to the public. This is not sufficient:

12 With the **written description** of a genus, however, merely drawing a fence around
13 a perceived genus is not a description of the genus. One needs to show that one
14 has truly invented the genus, *i.e.*, that one has conceived and described sufficient
15 representative species encompassing the breadth of the genus. Otherwise, one has
16 only a research plan, leaving it to others to explore the unknown contours of the
17 claimed genus.

18 *AbbVie*, 759 F.3d at 1300 (emphasis in original). Having failed to disclose the contours of its
19 claims, AZL has failed to provide a description of their full breadth.

20 It is readily apparent that h53AON1 (SEQ ID NO: 29) is not representative of the full
21 breadth of AZL claims 15, 76, 78, and 100. These claims cover AONs that range up to 50 or 80
22 unspecified nucleotides in length, even though h53AON1 is only 18 nucleotides in length (and
23 the maximum length disclosed for *any* AON disclosed in the ’495 application is only 24
24 nucleotides). (Exh. 2041 at 15; Exh. 2081 at § IV.A.) The claims cover AONs that have
25 thymine (T) bases or non-natural bases, even though h53AON1 contains *only* the natural
26 nucleobases adenine (A), cytosine (C), guanine (G), and uracil (U) (like all of the other AONs

disclosed in the '495 application). The claims cover large families of AONs that have morpholino, LNA, PNA, and hybrid chemical backbones, but h53AON1 has exclusively 2'-O-Me-PS modifications (like all of the other AONs disclosed in the '495 application). The claims cover AONs with Watson-Crick mismatches, but h53AON1 is perfectly complementary to the dystrophin gene (like all of the other AONs disclosed in the '495 application). (Exh. 2041 at 15, Table 2.) In sum, h53AON1 is not representative of the enormous number of chemical compounds potentially encompassed by each of independent claims 15, 76, 78, and 100 of the '495 application. (Exh. 2081 at ¶¶ 278-326.)

2. The '495 Application Does Not Disclose Structural Features Common to the Members of the Claimed Genera

The '495 application also fails to disclose structural features common to the claimed genera that are capable of inducing skipping of exon 53. *See Ariad*, 598 F.3d at 1350. Short of empirically testing each AON, a skilled person would have no way of knowing whether a particular AON would be capable of inducing skipping of exon 53. Numerous publications from the AZL group and others explain that a “trial and error procedure” is involved in identifying exon skipping AONs. (*E.g.* Exh. 2014 at 548.) Adding or removing nucleotides, backbone modifications, internucleotide linkage modifications, mismatches, and target cell type all influence exon skipping. (*See* § IV.B. above; Exh. 2081 at ¶¶ 68-86.)

The only common structural feature of “comprising” claims 15 and 76 is that they include at least 15 nucleobases of the nucleobase sequence of h53AON1 (claim 15) or all 18 of those nucleobases (claim 76). (Exh. 2081 at ¶¶ 296-98, 311-14.) But the specification does not provide any teaching permitting the skilled person to visualize all of the species (or even any of them) extending beyond 18 nucleobases that retain the capability of inducing skipping of exon 53. These claims fail for the same reason that h53AON1 as a single species cannot support a

1 genus claim encompassing trillions of species in an unpredictable technology: the h53AON1
2 nucleobase sequence does not adequately represent the genus of claimed compounds. (*See*
3 § V.A.1, above.) Indeed, to show that the AZL inventors possessed the subject matter they
4 claim, a person of ordinary skill reading the specification must be able to envision the structural
5 features critical for inducing skipping of exon 53 (such as length and chemical composition).
6 *See Ariad*, 598 F.3d at 1350 (“[A]n adequate written description requires a precise definition,
7 such as by structure, formula, chemical name, physical properties, or other properties, of species
8 falling within the genus sufficient to distinguish the genus from other materials.”). The ’495
9 application fails to provide any teaching on this point, much less a teaching that would permit a
10 person of ordinary skill to distinguish AONs that cause skipping versus those that do not.

11 The written description support for “capable of binding” claims 78 and 100 is equally
12 deficient, as these claims suffer from all of the deficiencies discussed above for the “comprising”
13 claims. (Exh. 2081 at ¶¶ 315-18.) Claim 78 recites that the AONs are “18 to 50 nucleotides in
14 length,” but provides no structure concerning the composition or nucleobase sequence of the
15 claimed AONs or even conditions for evaluating binding or skipping. Instead, the claims merely
16 recite that the AON “is capable of binding to an exon-internal sequence of exon 53.” But there is
17 no disclosure whatsoever in the ’495 application relating to structural features common to
18 species within claim 78 that would result in an AON (1) capable of binding to an exon-internal
19 sequence of exon 53 and (2) capable of inducing skipping of exon 53. Similarly, while claim
20 100 differs from claim 78 in requiring that the AON be “complementary to a consecutive part of
21 16 and 50 nucleotides of an exon internal sequence of exon 53,” the ’495 application does not
22 provide any teaching permitting a person of ordinary skill in the art to visualize members of the

1 genus meeting this limitation that are capable of inducing skipping of exon 53. (Exh. 2081 at
2 ¶¶ 323-26.)

3 As support for a common structural feature purportedly correlating with the function of
4 inducing exon skipping, AZL may seek to rely on the AON design rationale disclosed in
5 paragraphs [0006]-[0009] of the '495 application, which suggests that exon skipping AONs have
6 "overlap directed toward open and closed structures in the native exon RNA." (Exh. 2041 at
7 [0006].) Such an attempt must fail. First, none of the claims in the '495 application expressly
8 recite that the AONs are directed to open and closed structures of the dystrophin RNA (Exh.
9 2045), and there is no reason to read that limitation from the specification into the claims.
10 *SuperGuide Corp. v. DirecTV Enters., Inc.*, 358 F.3d 870, 875, (Fed. Cir. 2004) ("[I]t is
11 important not to import into a claim limitations that are not part of the claim."). Second, the
12 disclosed design rationale does not provide a structure, but instead provides a plan that a person
13 of ordinary skill in the art might use in attempting to identify the structure. But providing a mere
14 plan is insufficient. *Ariad*, 598 F.3d at 1350; *Eli Lilly*, 119 F.3d at 1566 ("An adequate written
15 description of a DNA . . . 'requires a precise definition, such as by structure, formula, chemical
16 name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical
17 invention.") (quoting *Fiers*, 984 F.2d at 1171)). Third, AZL presumably followed its plan in
18 creating h53AON2, yet that AON failed to even induce *in vitro* exon skipping. (Exh. 2041 at 15,
19 Table 2; Exh. 2081 at ¶ 278.) This highlights the lack of written description support for AZL's
20 broad genus claims.

21 **3. The Dependent Claims Do Not Narrow the Claims to Be**
22 **Commensurate with the Scope of the Description**

23 **a) Claims 77, 79, 80, and 101-103**

1 The dependent claims in the '495 application do not narrow the scope of the claims to be
2 commensurate with the scope of the description. Accordingly, these claims are also unpatentable
3 for lack of written description. Claims 77, 79, 80, and 101-103 recite additional limitations
4 relating to the length and/or nucleobase composition of the AONs. None of these dependent
5 claims place any additional limitations on chemical backbone, internucleotide linkages, or the
6 use of non-natural bases.

7 Claim 77 depends from claim 15 and limits the AON to 18 nucleotides having the base
8 sequence CUGUUGCCUCCGGUUCUG. (Exh. 2045 at 1.) Claim 77 provides no limits on the
9 possible modifications to the chemical backbone and internucleotide linkages embraced by the
10 claim. Conservatively, this claim covers hundreds of billions of different chemical compounds.
11 (Exh. 2081 at ¶ 200.) Yet only one of those compounds, h53AON1, is disclosed in the '495
12 application. That species is not representative of the full scope of the genus. (Exh. 2081 at
13 ¶ 295.) And the '495 application does not define any structural feature that correlates with the
14 ability of the AON to induce skipping of exon 53. (Exh. 2081 at ¶ 296.)

15 Claim 79 depends from claim 78, and requires that the “exon-internal sequence” contain
16 a “consecutive part of between 16 and 50 nucleotides” of exon 53, and that the AON is
17 complementary to that part. (Exh. 2045 at 2.) For a complementary sequence, however, the
18 '495 application allows for nucleobase mismatches. (Exh. 2041 at [0006]; Exh. 2081 at ¶¶ 137,
19 204.) Moreover, claim 79 still covers a tremendous number of AONs having different lengths,
20 nucleobase compositions, and modifications. (Exh. 2081 ¶¶ 218, 319.)

21 Claim 80 depends from claim 15, and requires that the AON be complementary to exon
22 53. (Exh. 2045 at 2.) As mentioned, the '495 application discloses that a sequence may have
23 mismatches with a target sequence and still be “complementary.” (Exh. 2041 at [0006].) Claim

1 80 is deficient because it places no additional limitations on AON length, chemical backbone,
2 internucleotide linkages, or the use of non-natural bases. (Exh. 2081 at ¶¶ 302-03.)

3 Claims 101 and 102 are multiple dependent claims that limit the AON to “less than 50
4 nucleotides in length” and “less than 80 nucleotides in length,” respectively. (Exh. 2045 at 3.)
5 Essentially, these claims only remove the longest AONs from the scope of the claims, and still
6 encompass a tremendous number of species. (Exh. 2081 at ¶¶ 225, 309.)

7 Claim 103 depends from claims 78 or 100, and recites that the AON “is capable of
8 binding without mismatches to said exon-internal sequence,” but still does not specify what the
9 exon-internal sequence is or under what conditions such binding must occur. (Exh. 2045 at 3;
10 Exh. 2081 at ¶¶ 226, 322.) Moreover, only one purportedly representative species is disclosed,
11 while the claim contains no meaningful limitation as to chemical backbone or internucleotide
12 linkages. As with the other dependent claims, the specification fails to disclose any structural
13 feature common to the members of the claimed genus that correlates with the functional
14 limitation of skipping exon 53. (Exh. 2081 at ¶¶ 226, 322.)

15 For these reasons, claims 77, 79, 80, and 101-103 are unpatentable for lack of written
16 description.

17 **b) Claims 82, 84, 86, 88-90, 97, and 98**

18 These claims fail to narrow the scope of the genus with respect to length or nucleobase
19 sequence, and encompass tremendous numbers of possible compounds. Claims 82, 84, and 86
20 recite certain modifications to the chemical backbone and/or internucleotide linkages. (Exh.
21 2045 at 2.) Claim 88 defines certain parameters for inducing skipping, and claims 89 (RT-PCR
22 and/or sequence analysis) and 90 (immunohistochemical and/or Western blot analysis) recite the
23 names of certain methods, at a very general level, that can be used for detecting skipping. (Exh.

2045 at 2; Exh. 2081 at ¶¶ 306-07, 462-64.) Claim 97 (DNA bases or RNA bases) limits the AON to the natural bases A, C, G, T, and U, but does not provide any additional limitation in terms of length, nucleobase sequence, mismatches, chemical backbone, or internucleotide linkages. (Exh. 2045 at 3; Exh. 2081 at ¶¶ 223-24, 321.) Claim 98 limits the AON to “RNA,” but does not provide any additional limitation for length, mismatches, or nucleobase sequence. (Exh. 2045 at 3; Exh. 2081 at ¶¶ 223-24, 308.) None of the limitations of these dependent claims narrow the genus of the claimed AONs to a scope commensurate with the description in the ’495 application. Therefore, claims 82, 84, 86, 88-90, 97, and 98 are unpatentable for lack of written description. (Exh. 2081 at ¶¶ 304-08, 321.)

B. The ’495 Application Fails to Enable a Skilled Person to Make and Use the Invention Without Undue Experimentation

Under 35 U.S.C. § 112(a), the ’495 application must enable a person of ordinary skill in the art to make and use the full scope of the claimed invention without undue experimentation. *In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988). A number of factors may be considered in assessing enablement, including (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art and the level of predictability in the art, (4) the level of one of ordinary skill, (5) the amount of direction provided by the inventor and the presence or absence of working examples, and (6) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *Id.*

A patent application must provide more than just a direction for further research: “Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. . . . Tossing out the mere germ of an idea does not constitute enabling disclosure.” *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997) (citation omitted).

1 The disclosure of the AZL applications would not enable a person of skill in the art to
2 make and use the claimed inventions without undue experimentation. The various claims of the
3 '495 application potentially cover a tremendous number of AONs with significant chemical
4 variability, but the applications disclose just a single AON capable of inducing *in vitro* skipping
5 for exon 53. Exon skipping is extremely unpredictable: changes to the nucleobase sequence,
6 chemical backbone, and internucleotide linkages of the AON all influence the ability of the AON
7 to induce exon skipping. (*See* § IV.B, above.) The quantity of experimentation required to
8 determine which AONs are capable of inducing exon 53 skipping *in vitro* is undue.

9 Further, neither the specifications nor declarations submitted in the AZL applications
10 provide clinical data or other evidence of *in vivo* therapeutic activity—a significant deficiency
11 for a nascent technology. *See In re '318 Patent Infringement Litig.*, 583 F.3d 1317, 1323-24
12 (Fed. Cir. 2009) (“If a patent claim . . . is not useful or operative, then it also fails to meet the
13 how-to-use aspect of the enablement requirement.”) (emphasis and citations omitted). The
14 quantity of experimentation needed to use the full scope of AZL’s claimed invention to treat
15 patients is staggering. In addition to testing a broad spectrum of nucleobase sequences, chemical
16 backbones, and internucleotide linkages, the skilled person would need to test the effect of each
17 such modification for therapeutic efficacy in patients. In the words of a paper co-authored by
18 members of the AZL group in 2005, “*significant development will be necessary to improve the*
19 *delivery aspects of AON before the antisense approach could be regarded as a realistic*
20 *therapeutic option in DMD.*” (Exh. 2025 at 450.)

21 **1. Breadth of the Claims / Unpredictability of the Art**

22 The breadth of the claims is addressed in § IV.D above and in Exhibit 2081 at § VI. In
23 brief, each of AZL’s involved claims encompasses tremendous numbers of possible chemical
24 compounds. This immense breadth is derived from (1) the varying ranges of possible AON

1 length; (2) the immense number of possible nucleobase sequence combinations; (3) the potential
2 for one or more “mismatches” with the target sequence; (4) the immense number of possible
3 chemical backbone modifications and (5) internucleotide linkage combinations; (6) the inclusion
4 of non-natural bases; and (7) the potential for other chemical modifications.⁴ (Exh. 2081 at
5 ¶¶ 388, 390-93.) Each of AZL’s claims also require that the claimed AONs are capable of
6 inducing exon 53 skipping, but fail to recite a cell type, cell source, or conditions for assessing
7 skipping, even though all of these parameters significantly and unpredictably influence exon
8 skipping. (Exh. 2081 at ¶¶ 66-67, 78, 403, 458-61.)

9 Like other antisense technologies, exon skipping with AONs is very unpredictable. *See*
10 § IV.B, above. In *Enzo Biochem*, the court relied on the “highly unpredictable” nature of
11 antisense technology in affirming a holding of unpatentability for lack of enablement. 188 F.3d
12 at 1372. The court cited inventor testimony that analogized the predictability of antisense
13 technology to “drilling for oil.” *Id.* Consistent with the lack of exon skipping drugs and AON
14 drugs generally, the court further cited a textbook explaining that “antisense strategies have not
15 been as universally straightforward or as easy to apply as was initially hoped.” *Id.* (citation
16 omitted).

⁴ To place some limit on claim scope, AZL may focus on the functional requirement that the claimed AONs be capable of inducing skipping of exon 53. But this is insufficient, because the skilled person must empirically test each AON to determine if it is capable of inducing exon skipping. (Exh. 2081 at ¶ 419.) “[T]he disclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility.” *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991).

1 As explained above, there is abundant evidence that exon skipping, an antisense
2 methodology, suffered from (and continues to suffer from) this same unpredictability. The AZL
3 group stated in a 2002 publication that they had “no insight” into targeting a sequence within a
4 folded RNA, and consequently “the effectivity of any designed AON, will therefore still have to
5 be tested empirically.” (Exh. 2010 at S76.) The ’495 application states that neither the length
6 nor the G/C content of the different tested AONs correlated to effectivity in exon skipping.
7 (Exh. 2041 at Table 2; *see also* Exh. 2010 at S76 (“There was no significant correlation between
8 length or sequence content of the AON and its effectiveness.”).) The UWA inventors similarly
9 stated in 2004 that “there was not a consistent trend that could be applied” to AON design, and
10 consequently “identification of the most effective . . . compounds has been the result of empirical
11 studies.” (Exh. 2049 at col. 27, ll. 54-59.) A 2007 paper co-authored by the AZL and UWA
12 groups stated that “several years after the first attempts at dystrophin exon skipping with
13 AO[N]s, ***there are still no clear rules to guide investigators in their design***, and in mouse and
14 human muscle cells *in vitro* there is great variability for different targets and exons.” (Exh. 2013
15 at 807.) That paper, and many others, further disclosed that different cell types are affected
16 differently by different AONs. (Exh. 2013 at 805.) As discussed above and in Dr. Wood’s
17 Declaration, small changes in length, nucleobase sequence, and chemical composition have
18 significant and unpredictable effects on exon skipping.

19 The AZL investigators possess more than an ordinary level of skill in the art. Yet only
20 one of their exon 53 targets was purportedly functional, even *in vitro*. (Exh. 2041 at 15.) And
21 their exon 51 clinical candidate, disclosed in the ’495 application, failed in its phase III clinical
22 trial. (Exh. 2039; Exh. 2081 at ¶ 431.)

1 **2. Amount of Direction / Quantity of Experimentation**

2 The sole purported working example of an exon 53 AON in the '495 application,
3 h53AON1, is a 2'-O-Me-PS that is 18 nucleotides in length and contains exclusively the natural
4 nucleobases A, C, G, and U. (Exh. 2041 at 15.) A second AON designed to target an exon-
5 internal sequence of exon 53, h53AON2, was also 18 nucleotides in length, also contained a 2'-
6 O-Me-PS backbone, and also contained exclusively the natural nucleobases A, C, G, and U—yet
7 failed to induce skipping of exon 53. (Exh. 2041 at 15.) No explanation is offered for this
8 failure. (Exh. 2081 at ¶ 278.)

9 While all are claimed, no morpholino, LNA, PNA, or hybrid AON is disclosed. (Exh.
10 2081 at ¶ 414.) No AON containing a “mismatch” versus the target sequence is disclosed. No
11 AON containing a thymine (T) nucleobase or a non-natural base is disclosed. The AZL
12 applications do not disclose *any* AONs comprising a mixed backbone chemistry rather than all
13 2'-O-Me-PS. (Exh. 2081 at ¶¶ 137, 281, 417.) The AZL applications also do not disclose any
14 AONs that have more than one type of modification. (Exh. 2081 at ¶ 417.) The longest AON
15 disclosed in the AZL applications is only 24 nucleotides. (Exh. 2081 at ¶¶ 418.)

16 Yet each of the claims at issue potentially encompasses a tremendous number of
17 chemical compounds, and exon skipping is an unpredictable field. In order to determine whether
18 a given AON is capable of inducing exon skipping, even *in vitro*, one must therefore experiment
19 on each different AON. Even making and testing a small number of these compounds represents
20 a massive investment of time and effort. For example, synthesizing a 30-base morpholino AON
21 takes approximately two weeks. (Exh. 2081 at ¶ 423.) Hybrid AONs containing morpholinos
22 and non-natural bases could take longer. (Exh. 2081 at ¶ 423.) *In vitro* transfection and the
23 subsequent RT-PCR study conservatively take several days for a single cell type. (Exh. 2081 at
24 ¶ 423.) Thus, even *in vitro*, making and testing a single morpholino AON may take on the order

1 of three weeks. (Exh. 2081 at ¶ 423.) Because of the unpredictability of exon skipping,
2 practicing the full scope of the claimed invention would require synthesizing and testing each of
3 these compounds. This would require a tremendous and undue amount of experimentation.
4 (Exh. 2081 at ¶ 424.)

5 In *Wyeth & Cordis Corp. v. Abbott Laboratories*, 720 F.3d 1380, 1385 (Fed. Cir. 2013),
6 the court determined that in an unpredictable art, making and screening “each of at least tens of
7 thousands of candidate compounds constitutes undue experimentation.” The specification,
8 which disclosed only a single working example, was found to constitute “only a starting point for
9 further iterative research in an unpredictable and poorly understood field.” *Id.* at 1383, 1386.
10 Here, each and every one of AZL’s claims potentially encompasses tremendous numbers of
11 compounds, the compounds at issue are large and chemically and structurally diverse, and
12 making and testing each compound would require significant time and effort.

13 Similar to *Wyeth*, the AZL applications disclose a starting point for further iterative
14 research in an unpredictable field. Even synthesizing candidate compounds would, in and of
15 itself, require a tremendous quantity of experimentation, and in the case of hybrids with non-
16 natural bases, require unconventional and possibly untested synthetic schemes. (Exh. 2081 at
17 ¶ 425.) Putting those synthesis challenges aside, even *in vitro* testing of the compounds would
18 then collectively take an immense and undue amount of time and effort. Yet the AZL
19 application offers only a single exon 53 species without meaningful guidance about particular
20 chemical substitutions and how they might affect exon 53 skipping. (Exh. 2081 at ¶ 425.)
21 Notably, the AZL group argued in a 2014 letter submitted to the European Patent Office that a
22 prior art reference did not enable claims directed to skipping exon 53 because “exon skipping is
23 tissue specific,” yet the cited prior art disclosed only “one single [AON] directed against the

interior of exon 53” tested in an *in vitro* system. (Exh. 2084 at 3-4 (emphasis in original)).

Because the ’495 application does not enable the full scope of the claims, the Board should grant this motion.

C. The ’495 Application Fails to Describe or Enable Therapeutic AONs

The ’495 application is directed to the use of AONs to treat DMD. (Exh. 2041 at [0015-0017].) Indeed, this is the sole disclosed practical utility for the claimed compounds. But the AZL clinical data cast doubt that the ’495 application discloses therapeutically useful AONs. As discussed above, when the AZL group selected an exon 51 candidate to take into the clinic, they chose drisapersen, disclosed in the AZL applications as h51AON1. (Exh. 2036 at 1513; Exh. 2037 at 987; Exh. 2041, Table 2.) But drisapersen failed in a phase III clinical trial: it did not meet the primary endpoint of a statistically significant improvement in the 6MWT compared to placebo. (Exh. 2039; Exh. 2081 at ¶¶ 383, 431.)

Notwithstanding this clinical failure, the ’495 application has exceedingly broad claims apparently intended to cover a tremendous number of possible exon 53 skipping AONs, including those that can be used clinically. But the scope of AZL’s right to exclude cannot “overreach the scope of [its] contribution to the field of art as described in the patent specification.” *Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1353 (Fed. Cir. 2011) (alteration in original) (quotation omitted). AZL has not described or enabled claims of this scope. Where practical utility is concerned, “a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.” *Brenner v. Manson*, 383 U.S. 519, 536 (1966). AZL has provided only the outline for the search.

VI. Conclusion

For the reasons explained above, UWA requests that the Board grant this motion, enter judgment against AZL, and terminate this interference.

Respectfully submitted,

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APPENDIX 1
List of Exhibits

EXHIBIT	DESCRIPTION
2001	EXHIBIT NUMBER NOT USED
2002	EXHIBIT NUMBER NOT USED
2003	CV of Matthew J.A. Wood.
2004	S. J. Errington et al., "Target selection for antisense oligonucleotide induced exon skipping in the dystrophin gene." J. Gene Med., 5(6): 518-527 (2003).
2005	A. G. Douglas et al., "Splicing therapy for neuromuscular disease." M. Cell. Neurosc., 56: 169-185 (2013).
2006	D. A. Braasch et al., "Novel antisense and peptide nucleic acid strategies for controlling gene expression." Biochemistry, 41(14): 4503-4510 (2002).
2007	A. A. Koshkin et al., "LNA (Locked Nucleic Acids): Synthesis of the adenine, cytosine, guanine, 5-methylcytosine, thymine and uracil bicyclonucleoside monomers, oligomerisation, and unprecedented nucleic acid recognition." Tetrahedron, 54(14): 3607-3630 (1998).
2008	J. Summerton et al., "Morpholino antisense oligomers: design, preparation, and properties." Antisense Nucleic Acid Drug Dev., 7(3): 187-195 (1997).
2009	D. A. Braasch et al., "Locked nucleic acid (LNA): fine-tuning the recognition of DNA and RNA." Chem. Biol., 8(1): 1-7 (2001).
2010	A. Aartsma-Rus et al., "Targeted exon skipping as a potential gene correction therapy for Duchenne muscular dystrophy." Neuromuscul. Disord., 12: S71-S77 (2002).
2011	S. M. Hammond et al., "Correlating In Vitro Splice Switching Activity With Systemic In Vivo Delivery Using Novel ZEN-modified Oligonucleotides" Mol. Ther.-Nucleic Acids, 2014 (in press).
2012	J. C. Van Deutekom et al., "Antisense-induced exon skipping restores dystrophin expression in DMD patient derived muscle cells." Hum. Mol. Genet., 10(15): 1547-1554 (2001).
2013	V. Arechavala-Gomez et al., "Comparative analysis of antisense oligonucleotide sequences for targeted skipping of exon 51 during dystrophin pre-mRNA splicing in human muscle." Hum. Gene Ther., 18(9): 798-810 (2007).
2014	A. Aartsma-Rus et al., "Guidelines for antisense oligonucleotide design and insight into splice-modulating mechanisms." Mol. Ther., 17(3): 548-553 (2009).
2015	B. Wu et al., "Targeted skipping of human dystrophin exons in transgenic mouse model systemically for antisense drug development." PloS one, 6(5): e19906 (2011).
2016	A. Aartsma-Rus et al., "Functional analysis of 114 exon-internal AONs for targeted DMD exon skipping: indication for steric hindrance of SR protein binding sites." Oligonucleotides, 15(4): 284-297 (2005).
2017	C. J. Mann et al., "Improved antisense oligonucleotide induced exon skipping in the mdx mouse model of muscular dystrophy." J. Gene Med., 4(6): 644-654 (2002).
2018	A. Aartsma-Rus et al., "Therapeutic antisense-induced exon skipping in cultured muscle cells from six different DMD patients." Hum. Mol. Genet., 12(8): 907-914 (2003).
2019	C. T. Fragall et al., "Mismatched single stranded antisense oligonucleotides can induce efficient dystrophin splice switching." BMC Med. Genet., 12(1): 141 (2011).
2020	H. A. Heemskerk et al., "In vivo comparison of 2'-O-methyl phosphorothioate and morpholino antisense oligonucleotides for Duchenne muscular dystrophy exon skipping." J. Gene Med., 11(3): 257-266 (2009).

EXHIBIT	DESCRIPTION
2021	Isis Pharmaceuticals Website: < http://www.isispharm.com/Pipeline/Therapeutic-Areas/Other.htm >
2022	C. A. Stein, "Delivery of antisense oligonucleotides to cells: a consideration of some of the barriers." Chemistry Today, 32: 4-7 (2014).
2023	C. J. Mann et al., "Antisense-induced exon skipping and synthesis of dystrophin in the mdx mouse." Proc. Natl. Acad. Sci., 98(1): 42-47 (2001).
2024	M. Bremmer-Bout et al., "Targeted exon skipping in transgenic hDMD mice: A model for direct preclinical screening of human-specific antisense oligonucleotides." Mol. Ther. 10(2): 232-240 (2004).
2025	F. Muntoni et al., "128th ENMC International Workshop on 'Preclinical optimization and Phase I/II Clinical Trials Using Antisense Oligonucleotides in Duchenne Muscular Dystrophy' 22-24 October 2004, Naarden, The Netherlands." Neuromuscul. Disord., 15(6): 450-457 (2005).
2026	C. A. Stein et al., "Therapeutic oligonucleotides: the road not taken." Clin. Cancer Res., 17(20): 6369-6372 (2011).
2027	T. L. Jason et al., "Toxicology of antisense therapeutics." Toxicol. Appl. Pharmacol., 201(1): 66-83 (2004).
2028	K. Anthony et al., "Dystrophin quantification, Biological and translations research implications," Neurology, 83:1-8 (2014) (on-line preprint).
2029	X. Tian et al., "Imaging oncogene expression." Ann. N. Y. Acad. Sci., 1002(1): 165-188 (2003).
2030	P. A. 't Hoen et al., "Generation and characterization of transgenic mice with the full-length human DMD gene." J. Biol. Chem., 283(9): 5899-5907 (2008).
2031	L. J. Popplewell et al., "Comparative analysis of antisense oligonucleotide sequences targeting exon 53 of the human DMD gene: Implications for future clinical trials." Neuromuscul. Disord., 20(2): 102-110 (2010).
2032	E. Kaye, "Results of the Eteplirsen Phase 2b and Phase 2b Extension Study in Duchenne Muscular Dystrophy." Abstract for 8th Annual Meeting of the Oligonucleotide Therapeutics Society (2012).
2033	S. Cirak et al., "Exon skipping and dystrophin restoration in patients with Duchenne muscular dystrophy after systemic phosphorodiamidate morpholino oligomer treatment: an open-label, phase 2, dose-escalation study." Lancet, 378(9791): 595-605 (2011).
2034	Sarepta Therapeutics Press Release dated January 15, 2014.
2035	U.S. Patent Application Publication No. 2014/0213635.
2036	N. M. Goemans et al., "Systemic administration of PRO051 in Duchenne's muscular dystrophy." N. Engl. J. Med., 364(16): 1513-1522 (2011).
2037	T. Voit et al., "Safety and efficacy of drisapersen for the treatment of Duchenne muscular dystrophy (DEMAND II): an exploratory, randomised, placebo-controlled phase 2 study." Lancet Neurol., 13(10): 987-96 (2014).
2038	K. M. Flanigan et al., "Pharmacokinetics and safety of single doses of drisapersen in non-ambulant subjects with Duchenne muscular dystrophy: Results of a double-blind randomized clinical trial." Neuromuscul. Disord., 24(1): 16-24 (2014).
2039	Prosensa Press Release dated September 20, 2013.
2040	GlaxoSmithKline Press Release dated January 13, 2014.
2041	U.S. Patent Application Publication No. 2006/0147952.
2042	International Patent Application No. PCT/NL2003/000214.
2043	U.S. Patent Application Publication No. 2013/0072671.

EXHIBIT	DESCRIPTION
2044	Updated Filing Receipt mailed December 11, 2012, In U.S. Patent Application No. 13/550,210.
2045	Academish Ziekenhuis Leiden Clean Copy of Claims and Sequences submitted August 5, 2014, in Interference No. 106,007 (RES).
2046	U.S. Patent No. 8,455,636.
2047	Academish Ziekenhuis Leiden Clean Copy of Claims and Sequences submitted August 5, 2014, in Interference No. 106,008 (RES).
2048	U.S. Patent No. 7,807,816.
2049	U.S. Patent No. 7,960,541.
2050	Academish Ziekenhuis Leiden Clean Copy of Claims and Sequences submitted October 15, 2014, in Interference No. 106,013 (RES).
2051	U.S. Patent No. 8,486,907.
2052	U.S. Patent Application Publication No. 2014/0275212.
2053	Amendment Under 37 C.F.R. §1.312 - Notice of Allowance Mailed, dated September 19, 2014, submitted in U.S. Patent Application No. 14/248,279.
2054	Excerpts from the prosecution history of U.S. Patent Application No. 11/233,495.
2055	Excerpts from the prosecution history of U.S. Patent Application No. 13/550,210.
2056	Excerpts from the prosecution history of U.S. Patent Application No. 14/198,992.
2057	Excerpts from the prosecution history of U.S. Patent Application No. 14/248,279.
2058	J. R. Mendell et al., "Eteplirsén for the Treatment of Duchenne Muscular Dystrophy," Ann. Neurol., 74:637-647 (2013).
2059	J. R. Mendell et al., "Eteplirsén in Duchenne Muscular Dystrophy (DMD: 144 Week Update on Six-Minute Walk Test (6MWT) and Safety," presented at the 19th International Congress of the World Muscle Society, October 7-11, 2014, Berlin, Germany.
2060	GlaxoSmithKline Press Release dated January 19, 2011.
2061	P. Järver et al., "A Chemical View of Oligonucleotides for Exon Skipping and Related Drug Applications," Nucleic Acid Therapeutics, 24(1):37-47 (2014).
2062	Second Preliminary Amendment filed on January 3, 2013, in U.S. Patent Application No. 13/550,210.
2063	Response & Amendments filed on January 21, 2014, in U.S. Patent Application No. 13/550,210.
2064	Response & Amendments filed on May 12, 2014, in U.S. Patent Application No. 13/550,210.
2065	Claims from Application filed on December 22, 2010, in U.S. Patent Application No. 12/976,381.
2066	Preliminary Amendment filed on December 22, 2010, in U.S. Patent Application No. 12/976,381.
2067	Preliminary Amendment filed on November 7, 2008, in U.S. Patent Application No. 12/198,007.
2068	Claims from Application filed on September 21, 2005, in U.S. Patent Application No. 11/233,495.
2069	Preliminary Amendment filed on September 21, 2005, in U.S. Patent Application No. 11/233,495.
2070	Amendment filed on October 31, 2007, in U.S. Patent Application No. 11/233,495.
2071	Amendment filed on April 1, 2009, in U.S. Patent Application No. 11/233,495.
2072	Amendment filed on September 16, 2009, in U.S. Patent Application No. 11/233,495.

EXHIBIT	DESCRIPTION
2073	Amendment After Non-Final Action filed on June 24, 2010, in U.S. Patent Application No. 11/233,495.
2074	Amendment In Response to Advisory Action filed on March 14, 2011, in U.S. Patent Application No. 11/233,495.
2075	Excerpts from Antisense Drug Technology: Principles, Strategies, and Applications (Stanley T. Crooke ed., Marcel Dekker, Inc.) (2001).
2076	Applicant -Initiated Interview Summary and Notice of Allowance filed on May 19, 2014, in U.S. Patent Application No. 13/550,210.
2077	Amendments to the Claims filed on May 8, 2014, in U.S. Patent Application No. 11/233,495.
2078	Amendments to the Claims filed on May 12, 2014, in U.S. Patent Application No. 13/550,210.
2079	Amendments to the Claims filed on July 16, 2014, in U.S. Application No. 14/198,992.
2080	Office Action filed on September 27, 2013, in U.S. Patent Application No. 13/550,210.
2081	Declaration of Matthew J. A. Wood, M.D., D. PHIL.
2082	Sarepta Therapeutics Press Release dated August 15, 2011.
2083	Kinali et al., Local restoration of dystrophin expression with the morpholino oligomer AVI-4658 in Duchenne muscular dystrophy: a single-blind, placebo-controlled, dose-escalation, proof-of-concept study, Lancet Neurology, 8:918-928 (Oct. 2009).
2084	Response filed on October 21, 2014, in EP12198517.
2085	Response filed on June 26, 2014, in EP13160338.
2086	U.S. Patent Application No. 14/198,992 of AZL as filed.
2087	U.S. Patent Application No. 13/550,210 of AZL and Preliminary Amendment as filed.
2088	U.S. Patent Application Publication No. 2013/0072671 of AZL.
2089	U.S. Patent Application No. 12/976,381 of AZL and Preliminary Amendment as filed.
2090	U.S. Patent Application Publication No. 2011/0312086 of AZL.
2091	U.S. Patent No. 8,759,507 of AZL.
2092	U.S. Patent Application No. 12/198,007 of AZL as filed.
2093	U.S. Patent Application Publication No. 2009/0076246 of AZL.
2094	U.S. Patent No. 7,534,879 issued on May 19, 2009 to AZL.
2095	U.S. Patent Application No. 11/233,495 of AZL and Preliminary Amendment as filed.
2096	Terminal Disclaimer filed on July 15, 2014, in the AZL U.S. Application No. 14/198,992 over the AZL U.S. Application No. 13/550,210.
2097	Preliminary Remarks filed on March 6, 2014, in the AZL U.S. Patent Application No. 14/198,992.
2098	U.S. Patent Application No. 13/270,992 of UWA, Transmittal and Preliminary Amendment as filed.
2099	U.S. Patent Application Publication No. 2012/0029060 of UWA.
2100	U.S. Patent Application No. 12/837,359 of UWA, Application Data Sheet and Preliminary Amendment as filed.
2101	U.S. Patent Application Publication No. 2011/0015253 of UWA.
2102	U.S. Patent No. 8,232,384 issued on July 31, 2012 to UWA.
2103	U.S. Patent Application No. 11/570,691 of UWA, Transmittal and Preliminary Amendment as filed.
2104	U.S. Patent Application Publication No. 2008/0200409 of UWA.
2105	WO 2006/000057 of UWA.

<i>EXHIBIT</i>	<i>DESCRIPTION</i>
2106	U.S. Patent No. 5,138,045.
2107	U.S. Patent No. 6,312,900.
2108	U.S. Patent Application No. 14/248,279 of AZL, Track One Request and Application Data Sheet as filed.
2109	Terminal Disclaimer filed on August 7, 2014, in the AZL U.S. Patent Application No. 14/248,279 over the AZL U.S. Patent Application No. 11/233,495.
2110	Remarks filed on August 27, 2014, in the AZL U.S. Patent Application No. 14/248,279.
2111	U.S. Patent Application No. 13/271,080 of UWA, Transmittal and Preliminary Amendment as filed.
2112	U.S. Patent Application Publication No.2012/0022145.
2113	<i>Brown v. Fodor</i> , Interference No. 104,358, Paper No. 60 at p. 2 (BPAI 1999).

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